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Ozone Response Relationships in Healthy Nonsmokers[1-3]

THOMAS J. KULLE, LARRY R. SAUDER, J. RICHARD HEBEL, and MARIE D. CHATHAM

SUMMARY Significant concentration responses were observed in FVC, FEV_1, FEF_{25-75}, SGaw, IC, and TLC in 20 healthy, nonsmoking volunteers exposed randomly to 0.00, 0.10, 0.15, 0.20, and 0.25 ppm O_3. In addition, significant response changes for FVC, FEV_1, and FEF_{25-75} were shown with time over the 2-h exposure. Intermittent, heavy exercise ($\dot{V}_E$, 68 L/min) lasting 14 min was employed every 30 min during exposure. Inspection of the concentration and time response curves suggests that the threshold for the group response is at or below 0.15 ppm O_3. Six subjects experienced decreases >5% in FEV_1 or >15% in SGaw at 0.15 ppm. This concentration is only slightly higher than the 1-h O_3 National Ambient Air Quality Standard. A dose-related response was also seen for cough, nose and throat irritation, and chest discomfort. The work load, length of exposure, and individual sensitivity must be considered for establishing a safe O_3 exposure level.

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Introduction

Ozone (O_3), a respiratory irritant and the major oxidant in photochemical smog, has been shown to produce acute significant decrements in FVC and FEV_1 (4 to 13%) at concentrations of 0.35 to 0.40 ppm with light-to-moderate exercise (1–3). Increasing the work load ($\dot{V}_E$ from 30 to 49 L/min) resulted in significant reductions in FVC and FEV_1 (5 to 6%) at 0.30 ppm O_3 (4). In other studies using continuous or intermittent heavy exercise ($\dot{V}_E$ from 55 to 80 L/min), significant decreases in FVC and FEV_1 (6 to 14%) were observed at concentrations of 0.16 to 0.24 ppm (5–7). These lower concentrations, representative of many U.S. urban episodic levels, are of particular concern as they approach the present National Ambient Air Quality Standard for O_3 (0.12 ppm). Definitive data are lacking on the time response in pulmonary function measured at discrete intervals during exposure to low levels of O_3 as well as the responses in individual subjects. McDonnell and coworkers (5) focused on group responses to O_3 after 2-h exposures. Adams and associates (8) reported a significant effect of exposure time on pulmonary function at 0.30 ppm, but not at 0.20 and 0.40 ppm O_3.

The objectives of this study were to describe the concentration and time response relationships as reflected by changes in pulmonary function in healthy, nonsmoking volunteers throughout 2-h exposures to low levels of O_3 (0.0 to 0.25 ppm), evaluate individual sensitivity to O_3, and assess the association between the reported symptoms and function effects.

Methods

Exposure Facility

The environmentally controlled chamber was designed so that input air passed through high-efficiency particulate absolute and activated carbon filters. The ventilation rate of 8.5 m^3/min in an exposure room 2.1 × 4.3 × 2.5 m enabled a complete air change every 2.6 min. Temperature was maintained at 22.2 ± 0.5° C, and relative humidity was maintained at 50 ± 2%.

Ozone was produced by passing 100% O_2 through a water-cooled, silent-arc, ultraviolet O_3 generator and introduced via stainless steel tubing into the air supply duct of the exposure room. The O_3 concentration in the chamber was continuously monitored using an ultraviolet absorption O_3 photometer (Model 1008-PC ozone analyzer; Dasibi, Glendale, CA) with self-contained calibrator unit, a gas phase chemiluminescent O_3 detector (Model 8410E ozone analyzer; Monitor Laboratories, San Diego, CA), and/or a microcoulomb O_3 sensor (Model 724-5 oxidant monitor; Mast Development Co., Davenport, IA). The Dasibi analyzer monitored all exposures and was calibrated during the study using similar units of the Maryland State Air Management Administration, Baltimore, and the National Bureau of Standards (NBS), Gaithersburg, MD. The calibrations agreed within ± 0.5% of the Maryland State unit and ± 2.0% of the NBS unit. In addition, calibration of the monitors was performed before and after each exposure using our Dasibi Model 1008-PC calibrator.

Subjects

The 20 subjects, all male nonsmokers, selected for the investigation had no history of chronic respiratory or cardiovascular disease with normal findings on physical examination. A nonsmoker was defined as one who had not smoked within the past 12 months and had a smoking history of less than 3 pack-years. This study was approved by the University of Maryland Human Volunteers Research Committee, and informed consent was obtained from each subject. The mean and standard deviation of these subjects for age, weight, and height were 25.3 ± 4.1 yr, 77.9 ± 11.1 kg, and 182.1 ± 6.7 cm, respectively.

Experimental Protocol

Each subject was exposed for 2 h in random order to 0.0, 0.10, 0.15, 0.20, and 0.25 ppm O_3. The exposures were separated by 1 wk to prevent adaptation (3) and were conducted at the same time each day to eliminate the influence of diurnal variation in pulmonary function (9). During the 2-h exposures, the exercise protocol consisted of 4 cycles of 14-min treadmill exercise alternated with 16 min of rest. The treadmill speed and grade necessary to produce a minute ventilation (V_E) of 15 times the subject's FEV_1 was determined prior to the study, and minor adjustments of the work load were occasionally made during the study to maintain this ventilation. The target $\dot{V}_E$ for the 20 subjects averaged 70.2 ± 9.6 L/min (mean ± SD).

Minute ventilation was measured with a 120-L gasometer (Warren E. Collins, Braintree, MA) at 4, 9, and 13 min during each exercise stint. Heart rate (HR) was monitored using an electrocardiographic telemetry system (Hewlett-Packard, Corvallis, OR).

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[1] From the Department of Medicine, University of Maryland, Baltimore, Maryland.

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[3] Requests for reprints should be addressed to Dr. Thomas J. Kulle, University of Maryland, Department of Medicine, Greene Street Building Room 414, 29 South Greene St., Baltimore, MD 21201.

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Measurements of airway resistance and thoracic gas volume were made prior to (t = 0 h) and after (t = 2 h) each exposure. These were determined with a modification (10) of the whole-body pressure plethysmographic technique of Dubois and associates (11, 12). The plethysmographic data were analyzed by means of a computer, and the results reported are based on an average of 20 to 30 panting breaths. Airway resistance was measured between flows of + 0.5 L/s inspiratory to −0.5 L/s expiratory. Each airway resistance measurement was converted to specific airway conductance (SGaw) to provide a volume-standardized measurement. Thoracic gas volume was measured at functional residual capacity (FRC).

Spirometric measurements (FVC, FEV_1, FEF_{25-75}) were made 9 min after each 14-min exercise stint using a 10-L Stead-Wells spirometer interfaced with an Eagle I microprocessor (Warren E. Collins). During each 2-h period, measurements were taken at t = 0, 23, 53, 83, and 113 min. The specifications for the measurements met the criteria set forth by the American Thoracic Society (13). A minimum of 3 technically acceptable forced expiratory maneuvers was obtained. The 2 maneuvers with the highest sum of FVC and FEV_1 were used to determine the mean FVC, FEV_1, and FEF_{25-75}.

Total lung capacity (TLC) was determined as the sum of FRC and inspiratory capacity (IC), and residual volume (RV) was determined as the difference between TLC and FVC. All volumes were expressed in liters at BTPS.

Subjective data in the form of symptoms were collected at the end of each exposure day. The symptom questionnaire contained 6 questions regarding the presence and severity of cough, eye irritation, nose or throat irritation, sweating, headache, and chest discomfort or tightness. The subjects classified their response to each symptom as none, mild (present, but not annoying), moderate (annoying), or severe (debilitating). For statistical analysis, a score of 1 was assigned to none, 2 to mild, 3 to moderate, and 4 to severe.

Statistical Methods

The least squares curve fitting and analyses of variance were employed to determine the concentration-response relationships between O_3 and the measures of pulmonary function. The response at a given time (R_t) was defined as the ratio of the value of the measure at that time (F_t) to the value at time zero (F_0); i.e., $R_t = F_t/F_0$. Then, $(1- R_t)100$ gives the percent reduction in pulmonary function at time t.

With R_t as the dependent variable, an analysis of variance was performed to determine if there was a significant concentration and/or time effect for a given measure of pulmonary function. The sources of variation and the degrees of freedom available for each in the analyses of variance for FVC, FEV_1, and FEF_{25-75} are indicated in table 1. Similar analyses were done for SGaw, FRC, IC, and TLC without the time factor, because these functions were measured only at t = 0 and 120 min.

TABLE 1

SOURCES OF VARIATION AND DEGREES OF FREEDOM IN ANALYSIS OF VARIANCE

Source of Variation	Degrees of Freedom
Concentration	4
Linear	1
Nonlinear	3
Time	3
Concentration × Time interaction	12
Linear	3
Nonlinear	9
Subjects	19
Concentration × Subjects interaction	76
Linear	19
Nonlinear	57
Time × Subjects interaction	57
Concentration × Time × Subjects interaction	228
Linear	57
Nonlinear	171

The analysis of variance established: (*1*) whether there was a concentration effect, (*2*) if present, does this effect vary with the time course of exposure, and (*3*) does the concentration effect and its time course dependence vary substantially from subject to subject. Where a significant concentration effect was found for a given pulmonary function, a least squares curve was fitted to the observed concentration responses for each time point. The following model was used: $R_t = (a + be^{cx})^{-1}$ or Percent Reduction in Function (Y) = $100[1- (a + be^{cx})^{-1}]$ where, x = O_3 concentration (ppm); e = the exponential constant (2.718); a, b, and c = the constants found by fitting the observed data.

This model was chosen because it describes a curve that is typical of dose-response relationships, and because a linearizing transformation is available for it by redefining the dependent variable as $1/R_t$ and the independent variable as e^{cx}. The constants a and b were found by first assuming a value for c and then fitting the linear version of the model by least squares. To find the value of c that provided the best fit, this procedure was repeated with new values of c until the sum of squares for the nonlinear concentration effect component of the analysis of variance (see table 1) reached a minimum.

Results

Daily O_3 concentrations in the study were maintained at 0.105 ± 0.002, 0.153 ± 0.003, 0.205 ± 0.004, and 0.254 ± 0.003 ppm (mean ± SD). During the period beginning 1 wk prior to the study until its completion (January to May 1983), the daily maximal 1-h concentrations of atmospheric O_3 measured in Baltimore by the Maryland State Air Management Administration averaged 0.033 ± 0.017 ppm.

The mean $\dot{V}_E$ and HR over all exercise periods and O_3 concentrations were 67.8 ± 8.2 L/min and 157 ± 10.3 beats/min, and were not significantly different in any of the 5 exposures. Individual $\dot{V}_E$ values ranged from 51.1 to 85.4 L/min, and HR determinations ranged from 137 to 174 beats/min. Treadmill speeds ranged between 2.5 and 4.5 mph with elevations between 7.0 and 15.0% grade. The mean work load for the 20 subjects was 758 ± 140 kg-m/min.

Preexposure measurements of pulmonary function over the 5 exposure sessions showed no systematic difference. Similarly, there were no significant changes from preexposure when the subjects breathed clean air over the 2-h period (table 2).

Group mean pulmonary function measurements are presented in table 2, with response curves for percent reduction in FVC and FEV_1 over both O_3 concentration and exposure time shown in figure 1A and B. The decrement in FVC, FEV_1, and FEF_{25-75} increased with O_3 concentration over fixed time periods of exposure. For each O_3 concentration, the response with exposure time was linear for FVC (figure 2A), FEV_1 (figure 2B), and FEF_{25-75}. The overall response for these spirometric functions was exponential with concentration and linear with time. The improvement (negative percent reduction) in FEV_1 seen at the lowest O_3 concentrations (figures 1B and 2B) is believed to be an exercise effect producing airway dilatation. Inspiratory capacity and TLC also signifi-

TABLE 2

PULMONARY FUNCTION MEASUREMENTS WITH OZONE EXPOSURE*

	O_3 Concentration, ppm				
	0.00	0.10	0.15	0.20	0.25
FVC, L					
t = 0	5.39 ± 0.77	5.39 ± 0.70	5.41 ± 0.72	5.45 ± 0.74	5.47 ± 0.74
t = 23	5.38 ± 0.78	5.38 ± 0.74	5.39 ± 0.71	5.43 ± 0.75	5.36 ± 0.73
t = 53	5.35 ± 0.76	5.38 ± 0.74	5.42 ± 0.71	5.37 ± 0.75	5.28 ± 0.73
t = 83	5.35 ± 0.72	5.38 ± 0.75	5.36 ± 0.71	5.30 ± 0.72	5.16 ± 0.76
t = 113	5.36 ± 0.74	5.37 ± 0.72	5.34 ± 0.70	5.25 ± 0.74	5.08 ± 0.74
FEV_1, L					
t = 0	4.58 ± 0.65	4.58 ± 0.58	4.58 ± 0.61	4.61 ± 0.63	4.62 ± 0.60
t = 23	4.65 ± 0.63	4.61 ± 0.59	4.59 ± 0.59	4.64 ± 0.62	4.59 ± 0.59
t = 53	4.64 ± 0.62	4.61 ± 0.61	4.60 ± 0.59	4.58 ± 0.63	4.52 ± 0.62
t = 83	4.64 ± 0.60	4.62 ± 0.62	4.56 ± 0.61	4.50 ± 0.62	4.38 ± 0.64
t = 113	4.64 ± 0.62	4.63 ± 0.60	4.55 ± 0.58	4.46 ± 0.63	4.31 ± 0.63
FEF_{25-75}, L/s					
t = 0	5.19 ± 1.16	5.12 ± 1.09	5.16 ± 1.22	5.08 ± 1.10	5.19 ± 1.14
t = 23	5.08 ± 1.07	4.86 ± 1.03	4.87 ± 1.16	4.96 ± 1.08	4.91 ± 1.09
t = 53	5.07 ± 1.04	4.88 ± 0.99	4.83 ± 1.11	4.88 ± 1.09	4.80 ± 1.14
t = 83	5.06 ± 1.08	4.91 ± 1.07	4.80 ± 1.15	4.75 ± 1.12	4.57 ± 1.19
t = 113	5.06 ± 1.04	4.93 ± 1.14	4.84 ± 1.11	4.68 ± 1.14	4.60 ± 1.26
SGaw, $(cmH_2O \times s)^{-1}$					
t = 0	.179 ± .042	.186 ± .053	.175 ± .040	.180 ± .048	.179 ± .048
t = 120	.170 ± .038	.174 ± .050	.164 ± .042	.156 ± .044	.152 ± .043
FRC, L					
t = 0	3.89 ± 0.75	3.87 ± 0.66	3.73 ± 0.65	3.83 ± 0.67	3.84 ± 0.72
t = 120	3.95 ± 0.82	3.99 ± 0.77	3.84 ± 0.73	3.82 ± 0.77	3.95 ± 0.78
IC, L					
t = 0	3.52 ± 0.62	3.56 ± 0.53	3.64 ± 0.56	3.65 ± 0.55	3.59 ± 0.56
t = 120	3.53 ± 0.57	3.52 ± 0.49	3.49 ± 0.52	3.36 ± 0.51	3.26 ± 0.60
TLC, L					
t = 0	7.41 ± 1.02	7.43 ± 0.81	7.37 ± 0.83	7.47 ± 0.89	7.43 ± 0.91
t = 120	7.48 ± 0.96	7.51 ± 0.91	7.33 ± 0.91	7.18 ± 0.99	7.21 ± 1.06

Definition of abbreviations: FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; FEF_{25-75} = forced expiratory flow rate between 25 and 75% FVC; SGaw = specific airway conductance; FRC = functional residual capacity; IC = inspiratory capacity; TLC = total lung capacity; t = time of exposure in minutes.

* Values are means ± SD.

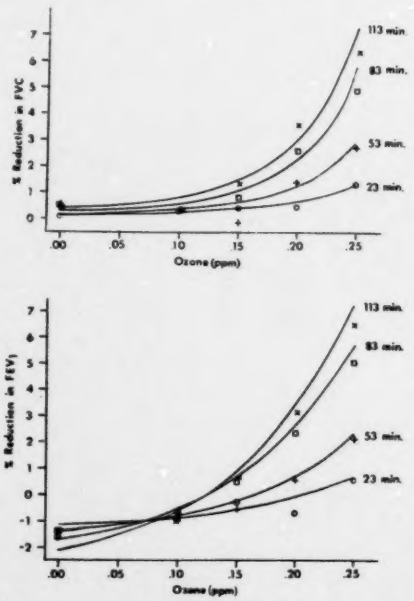

Fig. 1. Group mean O_3 concentration-response curves for percent reduction in FVC (A) and FEV_1 (B) at specific exposure time periods.

cantly decreased with increasing levels of ozone, with no changes in RV or FRC. The percent fall in SGaw with increasing O_3 concentrations exceeded those for either FVC or FEV_1, i.e., 14.9 versus 6.4% for FVC and FEV_1 with 2-h exposure to 0.25 ppm O_3.

The mathematical model constants a, b, and c determined for the fitted concentration-response curves of FVC, FEV_1, FEF_{25-75}, SGaw, IC, and TLC are presented in table 3. The levels of significance for the various concentration-response effects are shown in table 4. With the transformation model described previously and selection of the dependent and independent variables shown in table 4 for each pulmonary function, a significant linear concentration effect ($p < 0.01$) was demonstrated for FVC, FEV_1, FEF_{25-75}, SGaw, IC, and TLC, but not for FRC. Because the nonlinear concentration effects were small and not significant, a good fit to the model is indicated.

As shown in table 4, the significant

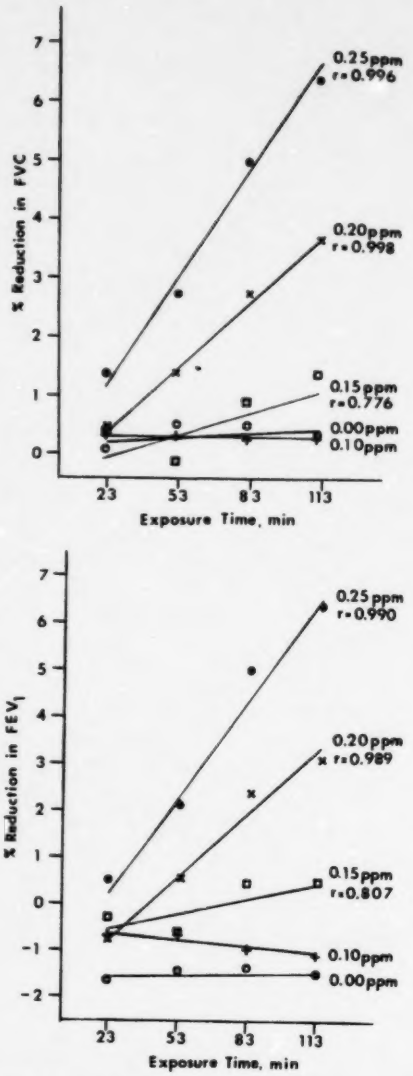

Fig. 2. Group mean time-response curves for percent reduction in FVC (A) and FEV_1 (B) at specific O_3 exposure concentrations.

Concentration × Time interaction verified that the concentration-response curve changed with exposure time for FVC and FEV_1 (figure 2A and B) as well as for FEF_{25-75}. Subjects × Concentration and Subjects × Concentration × Time interactions demonstrated significant individual variation in concentration and time responses within the study population. Significant individual variation in response with concentration also occurred for SGaw, IC, and TLC.

As a result of the variation in response between subjects, the percent decrement in FEV_1 and SGaw after 2 h exposure at each O_3 concentration was assessed for each individual subject (figure 3). A greater than 5% decrease in

TABLE 3

CONSTANTS FOR CONCENTRATION-RESPONSE CURVES USING EQUATION

$$Y = 100\left(1 - \frac{1}{a + be^{cx}}\right)$$

Pulmonary Function	Time (min)	a	b	c
FVC	23	1.002	0.000079	20
	53	1.002	0.000190	
	83	1.003	0.000392	
	113	1.004	0.000509	
FEV_1	23	0.987	0.00150	10
	53	0.983	0.00329	
	83	0.976	0.00694	
	113	0.971	0.00869	
FEF_{25-75}	23	1.035	0.0018	10
	53	1.029	0.0048	
	83	1.016	0.0111	
	113	1.014	0.0116	
SGaw	120	1.029	0.0132	10
IC	120	0.933	0.0541	5
TLC	120	0.961	0.0242	5

Definition of abbreviations: For FVC, FEV_1, FEF_{25-75}, SGaw, IC, and TLC, see table 2; Y = % reduction in pulmonary function; x = ozone concentration, ppm; e = exponential constant, 2.718; a, b, and c = constants found by fitting the observed data.

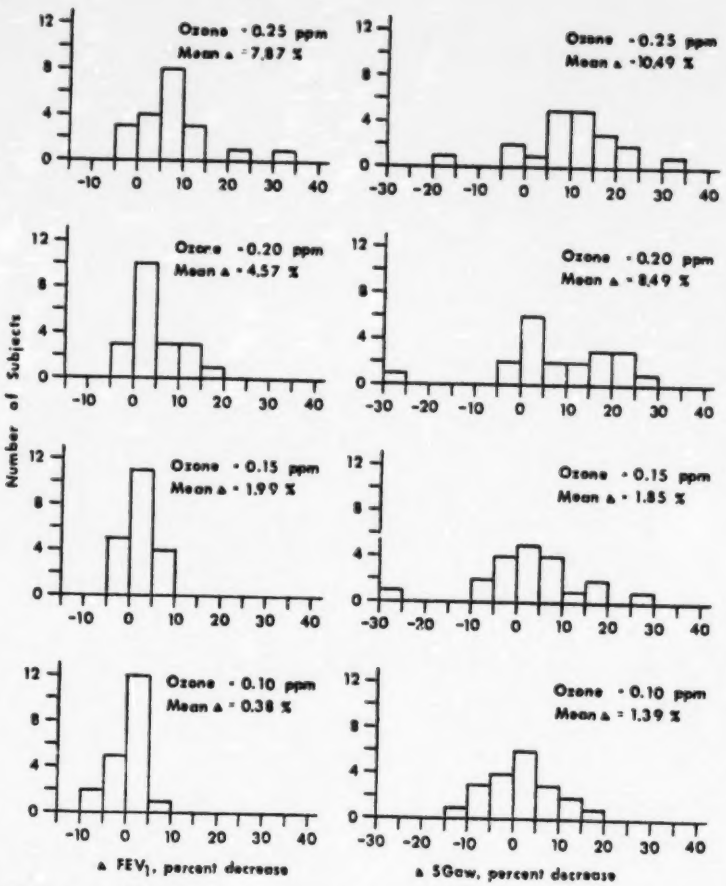
Ozone - 0.25 ppm
Mean Δ - 7.87 %
Ozone - 0.25 ppm
Mean Δ - 10.49 %
Ozone - 0.20 ppm
Mean Δ - 4.57 %
Ozone - 0.20 ppm
Mean Δ - 8.49 %
Ozone - 0.15 ppm
Mean Δ - 1.99 %
Ozone - 0.15 ppm
Mean Δ - 1.85 %
Ozone - 0.10 ppm
Mean Δ - 0.38 %
Ozone - 0.10 ppm
Mean Δ - 1.39 %
Number of Subjects
Δ FEV1, percent decrease
Δ SGaw, percent decrease

Fig. 3. Histograms of individual responses (percent decrease from control) in FEV_1 and SGaw with 2-h exposures to 0.10, 0.15, 0.20, and 0.25 ppm O_3.

FEV_1 was experienced by 1 subject at 0.10 ppm, 4 subjects at 0.15 ppm, 7 subjects at 0.20 ppm, and 13 subjects at 0.25 ppm O_3. A similar response distribution resulted for SGaw. A greater than 15% decrease in SGaw was experienced by 1 subject at 0.10 ppm, 3 subjects at 0.15 ppm, 7 subjects at 0.20 ppm, and 6 subjects at 0.25 ppm O_3.

To further demonstrate the response variability observed between subjects, individual dose-response plots for FEV_1 are presented in figure 4. These responses were arbitrarily divided into 4 groups, i.e., none (< 5% decrease), mild (5 to 10% decrease), mild to moderate (10 to 15% decrease), and moderate to severe (>15% decrease). Included in the first group (<5% decrease) were 3 nonreactors showing improvement in function, e.g., S-17, and 5 subjects with an increasing but limited decrement in function, e.g., S-10. There were 7 subjects with a mild response, e.g., S-5, 3 with a mild-to-moderate response, e.g., S-14, and 2 with a moderate-to-severe response, e.g., S-18.

Cough, nose and throat irritation, and chest discomfort or tightness all demonstrated a significant dose-response relationship (table 5). At 0.25 ppm O_3, the symptoms reported ranged from none to severe for cough and none to moderate for nose and throat irritation and chest discomfort. Eye irritation and headache did not show any significant concentration effect. Consistent with the level of exercise, the mild to moderate sweating reported during all O_3 exposures demonstrated no dose effect. None of these symptoms were reported by any subject prior to entry into the environmental chamber. The reported symptom of cough correlated with the observed decrements in FVC and FEV_1 ($r = 0.52$, $p < 0.05$), nose and throat irritation correlated with FEV_1 changes ($r = 0.49$, $p < 0.05$) but not with FVC ($r = 0.37$, $p > 0.10$), with the weakest correlation for chest discomfort ($r = 0.35$, $p > 0.10$).

TABLE 4

SUMMARY OF F TEST ANALYSIS ON CONCENTRATION EFFECTS*

Pulmonary Function	Dependent Variable	Independent Variable	Statistical Significance of Effects: Main Concentration Effects, Linear	Main Concentration Effects, Nonlinear	Linear Interaction Effects: Conc × Time	Subject × Conc	Subject × Conc × Time
FVC	$1/R_t$	e^{cx}	$p < 0.01$	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$
FEV_1	$1/R_t$	e^{cx}	$p < 0.01$	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$
FEF_{25-75}	$1/R_t$	e^{cx}	$p < 0.01$	NS	$p < 0.01$	$p < 0.01$	$p < 0.01$
SGaw	$1/R_t$	e^{cx}	$p < 0.01$	NS	–	$p < 0.05$	–
FRC	R_t	X	NS	NS	–	NS	–
IC	$1/R_t$	e^{cx}	$p < 0.01$	NS	–	$p < 0.01$	–
TLC	$1/R_t$	e^{cx}	$p < 0.01$	NS	–	$p < 0.01$	–

Definition of abbreviations: R_t = pulmonary function response at time t; Conc = concentration. For other definitions, see table 3.

* F tests were performed in conjunction with the analysis of variance shown in table 1.

Discussion

The study reported herein and other

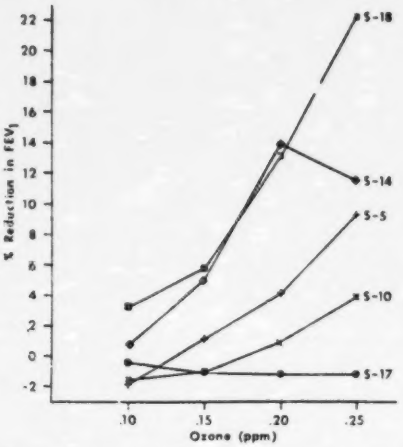

Fig. 4. Individual concentration-response plots (percent reduction from control) in FEV_1 with 2-h exposures to 0.10, 0.15, 0.20, and 0.25 ppm O_3. Four groups of observed responses were none (S-17 and S-10), mild (S-5), mild to moderate (S-14), and moderate to severe (S-18).

controlled clinical studies (5–7) exposing healthy nonsmokers to 0.16 to 0.20 ppm O_3 while performing heavy exercise ($\dot{V}_E$, 55 to 80 L/min) observed significant decrements in pulmonary function. These concentration levels approach the 1-h O_3 National Ambient Air Quality Standard of 0.12 ppm. In addition, this study provides definitive data describing a linear response with time at these low concentrations and demonstrates a broad range of individual responses.

Of the published controlled clinical studies, this study is most similar to the study of McDonnell and coworkers (5); however, there are some important differences in protocol. The study of McDonnell and coworkers employed intermittent heavy exercise ($\dot{V}_E$, 66 L/min), randomly assigned subjects to one of six 2-h ozone exposures (0.0 to 0.40 ppm O_3), and performed pulmonary function tests before and after exposure only. Our study also used intermittent heavy exercise ($\dot{V}_E$, 68 L/min) and exposed volunteers to similar O_3 levels; however, each subject acted as his or her own control and was randomly exposed to all O_3 concentrations (0.0 to 0.25 ppm). Further, spirometric measurements were made every 30 min during each 2-h exposure; thus, spirometric dose-response determinations could be made over both O_3 concentration and exposure time for the group and each individual subject.

The significant Concentration × Time interaction (table 4) indicates that the group linear time responses for FVC and FEV_1 (figure 2A and B) as well as FEF_{25-75} were significantly different for the O_3 concentrations studied. The slopes of the group time-response plots became progressively steeper with increasing levels of O_3, with 0.15 ppm being the lowest level at which a time response was demonstrated. This suggests that the threshold for the group response to O_3 was at or below 0.15 ppm O_3. Our study did not indicate how long the linear increase in function decrement at 0.15 ppm O_3 lasts beyond 2 h or how large a magnitude the decrement in function would attain.

Adams and associates (8), employing 18 separate concentration-duration protocols using oral breathing, observed with heavy exercise ($\dot{V}_E$, 66 L/min) a significant effect of exposure time on pulmonary function at 0.30 ppm, but not at 0.20 or 0.40 ppm O_3. Individual exposure durations were 30, 45, 60, or 75 min, with pulmonary function measured at the end of each exposure, not at discrete intervals during continuous exposure as recommended for generating time-response plots.

Based upon 1- and 2-h exposures to 0.37 and 0.75 ppm O_3 with intermittent light exercise ($\dot{V}_E$, 2x resting), nomograms were constructed by Bates and Hazucha (14) showing predicted decreases in FVC, FEV_1, and MMFR in nonsmokers over exposure durations as long as 2.5 h for concentrations from 0.1 to 1.2 ppm O_3. For those concentrations employed in our study (0.1 to 0.25 ppm), a linear response over time was predicted for each concentration, consistent with our observed results, with the predicted values at 0.25 ppm O_3 for 2 h being approximately 50 to 70% of the FVC, FEV_1, and FEF_{25-75} data of our study. The concentration at which the predicted time-response nomograms became nonlinear appears to be between 0.35 and 0.40 ppm O_3. Concentration-response nomograms for individual exposure times were not presented.

The large variation in response between subjects apparent in figures 3 and 4 is substantiated by the significant Subject × Concentration interaction for FEV_1 and SGaw (table 4). Subject sensitivity to 0.25 ppm O_3 (figure 4) ranged from 3 subjects with "slight improvement" in function (nonreactor, e.g., S-17 in figure 4) to 2 subjects with decrements in function ≥ 22% (highly reactive, e.g., S-18). An additional 5 subjects were classified as nonreactors with slight but increasing decrements in function (e.g., S-10), with the balance of 10 subjects demonstrating intermediate responses with FEV_1 decrements from 5 to 15% (e.g., S-5 and S-14). As previously noted, the threshold for the group mean response to O_3 is at or below 0.15 ppm. At this concentration, 3 individual subjects had FEV_1 decreases of 5.9, 6.3, and 8.1%, whereas 3 other subjects showed SGaw reductions of 17.7, 18.8, and 25.3% from the control value (0.0 ppm O_3).

This study is supportive of the hypothesis of McDonnell and coworkers that with heavy exercise the O_3-induced individual function changes are first manifested in the relatively narrow range between 0.18 and 0.24 ppm O_3 and that individual subjects will have a large range of response (5). Our study demonstrates that group mean and individual subject changes in function are first seen at or below 0.15 ppm O_3 and that a large range of individual responses to O_3 results (figures 3 and 4).

The developed model, $Y = 100[1 - (a + be^{cx})^{-1}]$, is representative of a physiologic dose-response curve. For the O_3 concentrations employed (0.0 to 0.25 ppm), the lower half of this curve was shown in the concentration response obtained for FVC, (figure 1A) and FEV_1 (figure 1B), i.e., consistently greater decrement with increasing O_3 concentrations without any plateau. McDon-

TABLE 5

SYMPTOM MEASUREMENTS WITH OZONE EXPOSURE*

	O_3 Concentration, ppm					Dose Effect Significance
	0.00	0.10	0.15	0.20	0.25	
Cough	1.00 ± 0.00	1.00 ± 0.00	1.20 ± 0.41	1.40 ± 0.50	1.65 ± 0.88	$p < 0.01$
Eye irritation	1.00 ± 0.00	1.00 ± 0.00	1.05 ± 0.22	1.10 ± 0.31	1.05 ± 0.22	NS
Nose/throat irritation	1.00 ± 0.00	1.05 ± 0.22	1.05 ± 0.22	1.35 ± 0.49	1.45 ± 0.69	$p < 0.01$
Sweating	2.25 ± 0.64	1.95 ± 0.51	2.10 ± 0.72	2.10 ± 0.55	2.00 ± 0.46	NS
Headache	1.10 ± 0.31	1.10 ± 0.31	1.05 ± 0.22	1.35 ± 0.49	1.10 ± 0.31	NS
Chest discomfort	1.00 ± 0.00	1.00 ± 0.00	1.10 ± 0.31	1.35 ± 0.59	1.30 ± 0.57	$p < 0.05$

* Values are means ± SD. Presence and severity of symptoms measured: 1 = none; 2 = mild (present, but not annoying); 3 = moderate (annoying); 4 = severe (debilitating).

nell and coworkers (5) obtained sigmoid-shaped dose-response curves for FVC and FEV_1 over O_3 concentrations from 0.0 to 0.4 ppm; however, exposures to 0.30 and 0.40 ppm O_3 were required for decrements in FVC and FEV_1 to plateau. This is consistent with the FVC and FEV_1 data of our study. Of note, Woolcock and coworkers (15) observed that the dose-response curve of the human airways to bronchial challenge described a sigmoidal function for percent FEV_1 fall versus inhaled histamine dose in 10 normal subjects, both smokers and nonsmokers.

In addition to the increasing function response with time seen for O_3 concentrations $\geq$0.15 ppm (figures 2A and B), O_3 concentration dominates over exposure duration, in agreement with the observations of Watanabe and associates (16) concerning pulmonary resistance changes in O_3-exposed cats. Group mean decrements in pulmonary function have been predicted as a function of effective dose, wherein the relative contribution of O_3 concentration to pulmonary function decrement is greater than that of $\dot{V}_E$, which is greater than that of exposure duration (4, 8, 17).

Individual subjects in our study did not show significant correlation between changes in SGaw and FVC ($r = 0.09$) or between changes in SGaw and FEV_1 ($r = 0.24$). Maximal decrements in FVC (15 to 32%) were measured in Subjects 11, 18, and 23 and in FEV_1 (19 to 33%) in Subjects 7, 18, and 23. Maximal SGaw decreases (24 to 30%) were observed in Subjects 6, 11, and 28. McDonnell and coworkers (5) also showed no significant correlation ($r = -0.16$) between changes in FVC and SRaw for individual subjects. The 2 different observed responses for FVC, FEV_1, and FEF_{25-75}, i.e., curvilinear (exponential) with O_3 concentration and linear with exposure time, as well as the lack of correlation between changes in SGaw and FVC or FEV_1, might be attributable to different mechanisms including the possibility of different O_3 rates reaching the target tissues. This study, however, was not designed to examine these possible mechanisms.

Significant concentration-response curves were obtained both for FVC and TLC, but not for RV. This suggests the decreases in FVC resulted primarily from decreased inspiratory effort probably coupled with the reported symptoms leading to incomplete inflation of the lungs. This decreased effort could be a result of stimulation of rapidly adapting irritant or other airway receptors preventing maximal inspiration, either involuntarily or because of associated symptoms with O_3 inhalation (4, 8, 18).

The symptoms of cough, nose and throat irritation, and chest discomfort observed in this study are similar to those reported previously (5, 6, 19). The severity of these symptoms increased with O_3 concentration, as demonstrated by significant dose effects, with cough being the most dominant, also observed by McDonnell and coworkers (5) and Adams and Schelegle (6). This symptom also correlated with observed decrements in FVC and FEV_1, whereas the less dominant symptoms of nose and throat irritation and chest discomfort (table 5) showed weaker correlations.

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